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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,979	11/05/2007	Antoni Torrens Jover	283726US0PCT	9435

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
04/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/565,979	TORRENS JOVER ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *25-28 and 31-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☒ Claim(s) *4-24, 29-30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :4/12/2006, 1/26/2006, 10/23/2007.

DETAILED ACTION

1. This application is a 371 of PCT/EP04/08508 filed 07/29/2004, which claims priority to Espana P200301813 filed 07/30/2003.

Claims 1-56 are pending.

Response to Election/Restriction

2. Applicant's election with traverse of Group I in the reply filed on January 16, 2009 is acknowledged. The traversal is on the ground(s) that the claims were not interpreted in light of the description and that a "special technical" feature was present. This is not found persuasive because the examiner showed that at least where B is methyl, the only difference over the prior art is the change of H to Methyl (recited as alkyl radical in the instant claims), this is not a special technical and makes it clear that applicants' core is not a contribution over the prior art. This is discussed further in the rejection below. The restriction requirement is made FINAL.

Group I, Claims 1-24, 29-30 drawn to compounds and compositions. If this group is elected, a further election of a single disclosed species of compound is also required. Further restriction based on the election may be made.

Objections

3. Claims 4-24, 29-30 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. Claim 4 depends from claim 3 which is multiple dependent claim, all subsequent claims depend from any one of the preceding claims, such that when claim 30 is reached, while an improper multiple dependent claim in its own right, it also depends from 21 different improper multiple dependent claims. See MPEP § 608.01(n). Accordingly, the claims 4-24, 29-30 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1–3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims refer to groups that "optionally at least monosubstituted" yet do not fully delineate the identity of said groups. The limits on the monopoly that is to be granted on such claims would not be known. If the groups are defined within the specification such a reference is improper as a claim should be self-contained and self-referential. See *Ex Parte Fressola* 27 USPQ2d 1608:

"The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. Claims in utility applications [1] that define the invention entirely by reference to the specification and/or drawings, so-called "omnibus" or "formal" claims, while perhaps once accepted in American patent practice, are properly rejected under Section 112 Para. 2 as failing to particularly point out and distinctly claim the invention. See MPEP Section 706.03(h) (5th ed., rev. 14, Nov. 1992); Landis, Mechanics of Patent Claim Drafting, Section 2 (1974). This analysis is limited to claims in utility applications. Plant patent claims are defined "in formal terms to the plant shown and described." Claims in design patents are recited in formal terms to the ornamental design "as shown" or, where there is a properly included special description of the design, the ornamental design "as shown and described." MPEP Section 1503.01.....The general rule is that the claims should be self-contained; that is, they should not expressly rely upon the description or drawing to give them meaning. . . . The terms "substantially as described" and the like, once much used in claims (GLASCOCK 1943 Section 5640) are now rarely seen. The Office disregards them in interpreting claims. . . . Claims consisting only in a reference to the disclosure, as "The features of novelty herein disclosed," are not allowed except in design cases.....A claim which refers to the specification defeats the purpose of a claim."

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO03/0100159 (cited on the IDS and ISR). The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

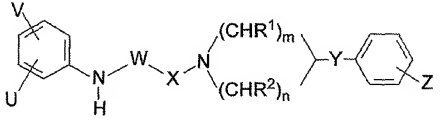
Determination of the scope and content of the prior art

(MPEP 2141.01)

WO03/0100159 teaches compounds of claim 1-3, as the Formula I (page 3 where W is CO, X is CH2 and Y is NR):

Detailed description of the invention

The present invention relates therefore first to new carboxylic acid amide derivatives of formula (I)



(I)

In the tables 5, & 6 shown below:

Table 5

Compounds of formula (I) prepared by procedure "B" described in Example 260 where X means -CH_2- group, both of -$(CHR^1)_m$- and -$(CHR^2)_n$- are -CH_2-CH_2- groups Y, Z, U and V are as given below:

No.	V	U	Y	Z	MW_c	MW_f	k'
15.	4- HO-	H-	$-CH_2-$	$4-CH_3-$	338.451	339.5	2.33
16.	4- HO-	H-	$CH_3-N<$	4-Cl-	373.884	374.4	1.369
17.	4- Ac-NH-	H-	$CH_3-N<$	4-Cl-	414.937	415.4	1.785
18.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	4-Cl-	450.985	451.5	1.704
19.	4- CH_3-SO_2-NH-	H-	$-CH_2-CH_2-$	4-F-	433.542	434.3	2.504
20.	4- Ac-NH-	H-	$-CH_2-CH_2-$	4-F-	397.494	398.2	2.53
21.	4- HO-	H-	$-CH_2-CH_2-$	4-F-	356.441	357.2	2.325
22.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	$4-CH_3-$	430.567	431.3	1.332
23.	4- Ac-NH-	H-	$CH_3-N<$	$4-CH_3-$	394.519	395.3	1.433
24.	4- Ac-NH-	H-	$CH_3-N<$	4-Br-	459.388	460.2	1.864
25.	4- HO-	H-	$CH_3-N<$	4-Br-	418.335	419.2	1.461
26.	4- CH_3-SO_2-NH-	H-	$CH_3-N<$	4-Br-	495.436	496.3	1.793
27.	4- HO-	H-	$CH_3-N<$	$4-CH_3-$	353.466	354.3	1.027

Table 6

Compounds of formula (I) prepared by procedure "B" described in Example 260 where X means $-CH_2-$ group, both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, U and V form together a bivalente group and Y and Z are as given below:

76.	3-4 -N=CH-NH-	CH_3-N<	4-Cl-	397.91	398.5	1.296
77.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-Cl-	428.92	429.5	1.896
78.	3-4 -S-C(SH)=N-	CH_3-N<	4-Cl-	447.015	447.5	2.285
79.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-Cl-	411.937	412.4	1.455
80.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-Cl-	426.948	427.4	1.937

82.	3-4 -O-CO-NH-	CH_3-N<	4-Cl-	414.893	415.5	1.827
83.	3-4 -CH=N-NH-	CH_3-N<	4-Cl-	397.91	398.5	1.853
84.	3-4 -NH-N=CH-	CH_3-N<	4-Cl-	397.91	398.5	1.932
85.	3-4 -CH=CH-NH-	CH_3-N<	4-Cl-	396.922	397.5	1.862
86.	3-4 -CH=C(CH_3)-NH-	CH_3-N<	4-Cl-	410.949	411.4	2.130
87.	3-4 -S-CO-NH-	CH_3-N<	4-Cl-	430.954	431.4	2.072

102.	3-4 -O-CO-NH-	CH_3-N<	4-CH_3-	394.475	395.2	1.467
103.	3-4 -NH-CO-O-	CH_3-N<	4-CH_3-	394.475	395.2	1.48
104	3-4 -NH-CO-NH-	CH_3-N<	4-CH_3-	393.491	394.2	1.423

105.	3-4 -CH_2-CO-NH-	CH_3-N<	4-CH_3-	392.503	393.3	1.444
106.	3-4 -N=CH-NH-	CH_3-N<	4-CH_3-	377.492	378.2	0.966
107.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-CH_3-	408.502	409.3	1.544
108.	3-4 -CH=CH-NH-	CH_3-N<	4-CH_3-	376.504	377.2	1.453
109.	3-4 -S-C(SH)=N-	CH_3-N<	4-CH_3-	426.597	427.3	1.896
110.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-CH_3-	406.53	407.3	1.574
111.	3-4 -NH-CS-NH-	CH_3-N<	4-CH_3-	409.552	410.3	1.455
112.	3-4 -S-CO-NH-	CH_3-N<	4-CH_3-	410.536	410.3	1.682
113.	3-4 -CH=C(CH_3)-NH-	CH_3-N<	4-Br-	455.4	456.2	2.211
114.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-Br-	456.388	457.2	1.522
115.	3-4 -CH_2-CH_2-CO-NH-	CH_3-N<	4-Br-	471.399	472.8	2.001
116.	3-4 -S-CO-NH-	CH_3-N<	4-Br-	475.405	476.2	2.159
117.	3-4 -CH=C(CH_3)-NH-	CH_3-N<	4-CH_3-	390.531	391.3	1.708
118.	3-4 -CH=N-NH-	CH_3-N<	4-CH_3-	377.492	378.3	1.495
119.	3-4 -NH-N=CH-	CH_3-N<	4-CH_3-	377.492	378.3	1.572
120.	3-4 -O-CO-NH-	CH_3-N<	4-Br-	459.344	460.2	1.913
121.	3-4 -CH_2-CO-NH-	CH_3-N<	4-Br-	457.372	458.2	1.839
122.	3-4 -N=CH-NH-	CH_3-N<	4-Br-	442.361	443.2	1.39
123.	3-4 -O-CH_2-CO-NH-	CH_3-N<	4-Br-	473.371	474.2	1.986
124.	3-4 -NH-N=CH-	CH_3-N<	4-Br-	442.361	443.2	2.023
125.	3-4 -CH=N-NH-	CH_3-N<	4-Br-	442.361	443.2	1.949
126.	3-4 -CH=CH-NH-	CH_3-N<	4-Br-	441.373	442.2	1.953
127.	3-4 -S-C(SH)=N-	CH_3-N<	4-Br-	491.466	492.2	2.371
128.	3-4 -NH-CS-NH-	CH_3-N<	4-Br-	474.421	475.2	1.897
129.	3-4 -NH-C(CH_3)=N-	CH_3-N<	4-CH_3-	391.519	392.3	1.151
130.	3-4 -NH-CO-O-	CH_3-N<	4-Br-	459.344	460.2	1.908

The compounds correspond to those of the instant claims where A is CH_2, R10 or R11 is a phenyl, heteroaryl with various substituents (i.e. the X of the prior art corresponds to the instant A, and the Z of the prior art corresponds to B or R1-R4).

Ascertainment of the difference between the prior art and the claims

It is clear that the prior art differs only in the individual compounds prepared. Numerous compounds of the instant claims are simple position isomers. Prior art compounds 15, 22-23, 27, 102-112, 117-119, 129, have a methyl group in the 4-position of the phenyl ring, while the instant claims have the methyl group in the 2-position. Other compounds of the instant claims may be seen as simply changing a hydrogen atom to a methyl group (i.e. the instant claims the group B is defined as not including H, but does include methyl).

(MPEP 2141.02)

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

The claims embrace numerous obvious variants of the species shown above, including H to Me conversion and position isomers. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use minor variants of those of the prior art to produce the instant invention. For cases involving analogs differing only in the interchange of a hydrogen for a methyl group, see *In Re Herr* 134 USPQ 176, *In re Wood*, 199 U.S.P.Q. 137 (C.C.P.A. 1978) and *In re Lahr*, 137 U.S.P.Q. 548, 549 (C.C.P.A. 1963), also discussed in *In Re*

Paquette 165 USPQ 317, "we also think it would be obvious to the person skilled in the art to provide dimers of an N-methyl-2-pyridone modified by the presence of a methyl substituent on one of the otherwise unsubstituted carbons of the ring. Since little could be more expected than that the resulting dimer would have two such substituents, that fact clearly does not detract from the obviousness of claims 15-18." See also *Ex parte Bluestone*, 135 USPQ 199 (Bd. Pat. App. & Int. 1961) finding that the N-methyl derivative of a prior art thiazolidinone unpatentably obvious and stated, citing *Ex parte Weston and Hamlin* with favor "A case nearly on all fours with this situation is *Ex parte Weston and Hamlin*, 121 USPQ 428 , wherein this Board held that mono substituted N' piperazines were not patentable over di-substituted piperazines of the reference because chemists are well aware of the difference between secondary and tertiary amines and their reactivities including the possibility of further substitution for the hydrogen in the secondary amine. This is the substitution that appellant has made in the Alvord compound."

Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these position isomers based on the expectation that such close analogues would have similar properties and upon the routine nature of such position isomer experimentation in the art of medicinal chemistry. It would be routine for the chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of

the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc. UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Claim Rejections - 35 USC § 112 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds where R^1-R^4 or B is $-CO_2R^{19}$, where R^{19} is H or alkyl (unsubstituted), $-(CH_2)R^{20}$, where R^{20} is H or alkyl (unsubstituted), halogen, alkyl (unsubstituted), alkoxy (unsubstituted), and hydroxy; R^5-R^9 are H or alkyl, R^{10} is H or alkyl, R^{11}

is phenyl where R is alkyl or phenyl, heteroaryl, tetrahydronaphthalene, indane, 1,3-benzodioxyl, which may be substituted with halogen, cycloalkyl, CH_2Ph, -CHOHR, OPh or in the case of those rings that are saturated oxo, it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents as claimed.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are very broad encompassing an extremely long list of prophetic groups bearing multiple substitutions (several pages). The working examples in the specification are numerous, however they are not representative of the genus claimed. In particular the variable B is only ever exemplified as $-CH_2OH$ or -C=OMe, However the variable is defined in the following manner in claim 1:

B represents an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted cycloaliphatic radical, a $COOR^{19}$-moiety, a $-(C=O)R^{20}$-moiety, or a $-CH_2OR^{23}$-moiety,

R^{19} represents hydrogen, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted cycloaliphatic radical, or an optionally at least mono-substituted aryl- or heteroaryl radical, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring-system,

R^{20} represents hydrogen, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted cycloaliphatic radical, an optionally at least mono-substituted aryl- or heteroaryl radical, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring-system, or a $NR^{21}R^{22}$-moiety,

R^{21} represents hydrogen, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted cycloaliphatic radical, or an optionally at least mono-substituted aryl- or heteroaryl radical, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring-system,

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R^{22} represents hydrogen, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted cycloaliphatic radical, or an optionally at least mono-substituted aryl- or heteroaryl radical, which may be condensed with an optionally at least mono-substituted mono- or polycyclic ring-system,

R^{23} represents hydrogen, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, which may comprise at least one heteroatom as a chain member, or a $-(C=O)R^{13}$-moiety,

R^{13} represents hydrogen, an unbranched or branched, saturated or unsaturated, optionally at least mono-substituted aliphatic radical, a saturated or unsaturated, optionally at least mono-substituted, optionally at least one heteroatom as ring member containing cycloaliphatic radical, which may be bonded via an optionally at least mono-substituted alkylene group and/or may be condensed with an optionally at least mono-substituted mono- or polycyclic ring-system, or an optionally at least mono-substituted aryl- or heteroaryl radical, which may be bonded via an optionally at least mono-substituted alkylene group and/or may be condensed with an optionally at least mono-substituted mono- or polycyclic ring-system,

The variables R^1-R^4, are only exemplified methyl, halogen, methoxy, or OH. The variable A is only exemplified as $-CH_2-$, and R^5-R^{10} are only every exemplified as hydrogen, yet have similar generic descriptions as that of B. The only substantial variation that takes place in the working examples is on the variable R^{11}, yet these variations (phenyl, quinoline, carbazole, dibenzofuran, tetrahydronaphthalene, fluorine, indane, and 1,3-benzodioxyl, which are substituted with halogen, cyclohexyl, CH_2Ph, -CHOHR –OPh or in the case of those rings that are saturated oxo) is not commensurate in scope with the claims.

This is a chemical invention requiring the synthesis of compounds and such compounds should have activity as Neuropeptide Y receptor ligands. In the NPY receptor drug design field it is well known that both changes to the electronic characteristics as well as the size of substituents markedly affects the utility of the compounds.

In the development of Neuropeptide Y ligands which also posses a piperidine core, which is that of the instant case, Jablonowski, J.A. et al. *Bioorganic and Medicinal Chemistry Letters* **2004**, *14*, 1239–1242, described the results of making such changes:

"This portion of the molecule also appeared to be sensitive to subtle changes in electronics, which were exemplified by significant differences in activity for compounds bearing the 2-pyridyl (27), 3-pyridyl (28) and 4-pyridyl (29) substitution. The 2- and 3-pyridyl analogues retain only minimal activity at the NPY Y2 receptor, while the 4-pyridyl binds modestly with IC50=12 mM. Oxidation of analogue 29 provided the 4- pyridyl-N-oxide analogue 30, which was inactive. Slight activity was also seen in the compound with 2-imidazolyl substitution as shown in analogue 31."

It is clear that the ability of these compounds to bind an NPY receptor, is highly unpredictable, and that such changes result in compounds that not only have reduced activity but actually do not have this activity all, which Jablonowski describes as inactive.

Finn J. et al *Bioorganic and Medicinal Chemistry Letters* **2002**, *12*, 1771–1774, who developed a series of NPY5 receptor ligands, came to the following conclusion:

"In summary, high-throughput synthesis proved valuable in the optimization of sulfonamide Y5 antagonists. **SAR trends vary with subtle changes to the ligand.** Analysis of the global data for sets of compounds is extremely useful in identifying different SAR trends for series of closely related compounds. It is notable that the SAR from the sulfonamide amine series did not translate to either the amide or urea series. Consequently, if one kept the optimal aryl sulfonamide and linking groups constant, the optimal amide and urea derivatives would have been missed. Inclusion of diversity groups (such as set f) illustrated the power of preparing compounds in sets. The unusual SAR for set f indicates a different mode of receptor-ligand interactions and present starting points for the discovery of alternative NPY Y5 specific ligands."(Emphasis added)

Leslie C. P. *Bioorganic and Medicinal Chemistry Letters* **2007**, *17*, 1043–1046, who also developed piperidine based NPY receptor ligands, noted that the reason for some of the observed that NPY 5 receptor binding is "highly demanding"

"Only the open-chain derivative 28 (Table 3) maintained a similar binding affinity, **suggesting that the binding pocket occupied by the piperazine is highly demanding in terms of the size and orientation of the amide substitutent which it can accommodate. Simple methylation of 28 is sufficient to give a fourfold drop in affinity.** The requirement for a basic amine in this region was confirmed by the inactivity of amide derivatives such as 25 and 32 (Tables 2 and 3, respectively)." (Emphasis added)

Poindexter G. S. et al. *Bioorganic and Medicinal Chemistry Letters* **2002**, *12*, 379–382 who also developed piperidine based NPY receptor ligands, states:

"The piperidine derivatives listed in Table 2 displayed Y1 binding potencies in the same range as the piperazines. Similarly, bis methyl ester substitution enhanced binding affinity relative to the asymmetric ethyl methyl ester derivative (6a, R1=CO2Et vs 6b, R1=CO2Me). Substitutions at the C-4 position on the piperidine ring with either aryl (6c, R2=2-MeOPh, 6d, R2=3-HOPh, and 6e, R2=3-MeOPh) or alkyl (6h, R2=c-hexyl) substituents were well tolerated; however, the simple, unsubstituted piperidine 6i (R2=H) was inactive in the assay, reflecting similar steric and/or lipophilic demands as the piperazines at this position."

Thus clearly this evidence shows that the requirements for NPY receptor binding are stringent, unpredictable and do not lead one to believe that the instant claims are operable over the majority of the scope claimed. The long list of the various optional groups includes very large groups, many basic and polar moieties and the evidence shows that these modifications would not lead to compounds that maintain utility. Even making the full scope of the compounds is undue experimentation as shown by statements of a skilled artisan, Derek Lowe, a Ph.D. medicinal chemist who has worked for numerous drug companies and runs the website "In the Pipeline" describes claims like those of the instant case in the following way:

"I've seen many claims that couldn't be fully enabled short of putting five hundred people to work on them full-time for about ten years." (In the Pipeline, online, accessed June 16, 2008,

"http://pipeline.corante.com/archives/2006/01/24/the_examiner_finally_snaps.php")

In order to practice the full scope of the invention, one of ordinary skill would not only need to create synthetic procedures *de novo*, but also decide what compounds to prepare. The specification gives very little guidance with regard to what the requirements for activity are i.e. which substituents would be preferred. In fact activity is only given for 10 compounds on page 106 of the specification. It is not obvious from the disclosure of these species, what other species will work. Certainly at least some compounds outside the scope exemplified, will work for example R11 was exemplified only as quinoline, benzofuran, and carbazole, yet it is believable that other heteroaryls in this position. Only hydrogen has been exemplified for several variables, yet one would expect alkyl analogs, for example methylated compounds to function the same. While working examples are not required, in nascent technologies, such as the instant case, the degree of unpredictability is an important factor. See MPEP 2164.02 for guidance regarding the size of claimed genus. See *Ex parte WEIL AND SCHLICHTING*, 158 USPQ 620 (Bd. Pat. App. & Int. 1967)

"We will sustain this rejection of the claims as we are in accord with the examiner's position. We find no support in the disclosure for such compounds encompassed by these claims wherein R 1, R 2, R 3, and R 5are all the same and selected from the group, lower alkyl , hydroxy , alkoxy , di(loweralkyl)amino and nitro for example. These claims appear to be in the nature of a paper concept wherein all possible substituents have been included in the composition. There are no examples of such compounds which are included within the vast scope encompassed by these claims, although appellants have a considerable disclosure with respect to certain components but this does not warrant claims of the enormous breadth recited."

In addition see *In re Fouche* 169 USPQ 429 which dealt with a similar issue with respect to how to use requirement of 112 1st paragraph,

"Both the examiner and the board noted that none of the working examples pertained to compounds wherein Z was heterocyclic. Appellant is quite correct in contending that, under our decisions in In re Robins, 57 CCPA 1321, 429 F.2d 452, 166 USPQ 552 (1970), the inclusion of

representative examples is not required to enable a person skilled in the art to use a generic invention. Nevertheless, an applicant must use some technique of providing teaching of how to use which is commensurate with the breadth of protection sought by the claim, unless such knowledge is already available to persons skilled in the art. It seems clear, and it is not disputed by appellant, that where an applicant undertakes to define his invention by the recitation of a Markush group, he must enable one skilled in the art to make and use at least one composition employing each member of the Markush group."

and *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976):

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

In re Walker, 22 USPQ (C.C.P.A. 1934)

"It is true, as argued by counsel, that appellant is entitled to claim not only the substance enumerated by him in his specification, but also their equivalents. However, in cases of this character, involving chemicals and chemical compounds, many of which of course differ radically in their properties, it must appear in the specification, either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that "the chemicals or chemical combinations included therein were generally capable of accomplishing the desired result." See In re Ellis, 37 App. D. C. 203; In re Dosselman, 37 App. D. C. 211; In re Langmuir, 20 C. C. P. A. (Patents) 733, 62 F. (2d) 93."

In Re Sus and Schaefer 134 USPQ 1962 301-310 (affirmed):

"It is, however, consistent with this public purpose embodied in the pertinent statutory requirement that the invention claimed shall be no broader than the invention set forth in the written description forming a part of the specification……thus it seems to us that one killed in this art would not be taught by written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only certain aryl radicals and certain specifically substituted aryl radicals would be suitable for such purposes."

It is the appropriate conclusion as shown by the state of the art in the NPY receptor drug development art that the full scope of the claims is not enabled. The examiner having established adequate reasons why a person skilled in the art could not use the genus as a whole without undue experimentation, has appropriately rejected the claims for scope of enablement. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has few working examples in this unpredictable art without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-3 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15, 19-21 of copending Application No. 10/566, 399. The claims overlap in scope. The '399 application is drawn only to compounds where in the instant claims R11 is carbazole. The instant claims are broader, however the variable R11 may be carbazole, in addition the working examples that have carbazole support a carbazole genus. This is a provisional obviousness-type double patenting rejection.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Janet L. Andres/
Supervisory Patent Examiner, Art Unit 1625